Out-of-hospital cardiac arrest in adults: lowering body temperature

Search date November 2014

Kendra Houston and Eddy S. Lang

ABSTRACT

INTRODUCTION: Post-resuscitation care after return of spontaneous circulation is critical to improving patient outcomes in sudden cardiac death. Therapeutic hypothermia has been a mainstay of treatment after successful cardiopulmonary resuscitation in the setting of ventricular fibrillation or pulseless ventricular tachycardia. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of lowering body temperature for comatose survivors of out-of-hospital cardiac arrest associated with ventricular tachycardia or ventricular fibrillation? We searched: Medline, Embase, The Cochrane Library, and other important databases up to November 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 222 studies. After deduplication and removal of conference abstracts, 114 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 89 studies and the further review of 25 full publications. Of the 25 full articles evaluated, one systematic review included in a previous version was updated and three RCTs were added at this update. We performed a GRADE evaluation for five PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for three interventions based on information about the effectiveness and safety of therapeutic hypothermia, different lower body temperatures, and different durations of lower body temperatures.

QUESTIONS

What are the effects of lowering body temperature for comatose survivors of out-of-hospital cardiac arrest associated with ventricular tachycardia or ventricular fibrillation? 4

INTERVENTIONS

LOWERING BODY TEMPERATURE FOR COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST

Likely to be beneficial

Therapeutic hypothermia (targeted temperature management) with or without standard therapy (including anti-arrhythmics) 4

Unknown effectiveness

Different lower body temperatures versus each other New 8

Different durations of lower body temperature versus each other New 11

Key points

- Pulseless ventricular tachycardia and ventricular fibrillation are the main causes of sudden cardiac death (SCD), but other ventricular tachyarrhythmias can occur without haemodynamic compromise.

  Ventricular arrhythmias occur mainly as a result of myocardial ischaemia or cardiomyopathies, so risk factors are those of cardiovascular disease (CVD).
- Cardiac arrest associated with ventricular tachyarrhythmias is managed with cardiopulmonary resuscitation and electrical defibrillation, where available.
- The previous version of this overview on out-of-hospital cardiac arrests examined a range of comparisons such as the effects of monophasic and biphasic shock, amiodarone, bretylium, and lidocaine.
- This updated overview focuses on therapeutic hypothermia (targeted temperature management to a body temperature of 36°C or lower and avoiding hyperthermia) with or without anti-arrhythmics.
- We have searched for evidence from RCTs and systematic reviews of RCTs on the effectiveness and safety of therapeutic hypothermia with or without anti-arrhythmics in people treated for out-of-hospital cardiac arrest.
- Controlled induction of moderate hypothermia after cardiac arrest has been shown to improve both survival and neurological outcomes in a population that typically carries a very poor prognosis.

  There is no clear indication from the systematic reviews whether one cooling method was superior to the other.

  There was no significant difference between pre-hospital cooling with cold IV fluids compared to standard care or in-hospital cooling in rates of survival to discharge. However, there was significant variability in the amount of IV fluids given in the pre-hospital setting; therefore, it is difficult to interpret the results.
- Regarding different lower body temperatures compared to each other, there was no significant difference in all-cause mortality and neurological outcomes when comparing a targeted temperature of 33°C with a targeted temperature of 36°C for a total of 36 hours. However, lowering body temperature to 32°C might be more effective than lowering to 34°C at reducing mortality at 6 months (based on the results of one small RCT).

  The ideal duration for targeted temperature management remains unclear.

Clinical context

GENERAL BACKGROUND

© BMJ Publishing Group Ltd 2015. All rights reserved.

The annual incidence of sudden cardiac death (SCD) has been estimated to approach 1/1000 in the population with a presumed cardiac aetiology. It is a critical condition that can result in death or severe neurological disability and constitutes a significant social and economic burden. Current standards of post-arrest treatment include therapeutic hypothermia (targeted temperature management), haemodynamic management (including vasopressor support), and percutaneous coronary intervention (PCI). Further routine management includes oxygenation and ventilation, with goals to avoid hyperventilation, and tight glucose control with aims to prevent both hyper- and hypoglycaemia. Overall, optimisation of post-arrest care is essential to improving chances of recovery. The goal of post-cardiac arrest treatment is rapid stabilisation, to improve organ perfusion, and to minimise tissue and organ damage.

FOCUS OF THE REVIEW

It is well established that performing early, high-quality chest compressions in the event of a cardiac arrest is one factor that has been consistently shown to improve patient outcomes. However, due to the difficulty of carrying out an RCT examining cardiac arrest care, there has been much debate over best practice for post-resuscitation protocols. It has been rationalised that therapeutic hypothermia can result in preserved brain function, and this has been a recommended standard of practice in post-resuscitation care with an aim to improve neurological outcomes. [1] Neurological injury has been recognised as a major cause of death in cardiac arrest patients. [2] Earlier trials have suggested that therapeutic hypothermia does have clinical benefit with respect to neurological outcomes in patients with a presumed cardiac-aetiology SCD. [3] [4] It has been hypothesised that a temperature less than 32°C is harmful, whereas 32°C to 35°C has looked promising. Furthermore, it has been proposed that earlier induction of hypothermia may have a positive impact on clinical outcomes. Historically, therapeutic hypothermia has been viewed as a valuable treatment relative to other important interventions, such as glucose control, goal-directed haemodynamic management, oxygenation, ventilation, and PCI. [1]

COMMENTS ON EVIDENCE

Numerous studies have examined therapeutic hypothermia compared to normothermia. Many studies utilised conventional cooling methods for attainment of hypothermia, and only one study used haemofiltration. The likely higher health care costs and intensive resources required for haemofiltration are important to bear in mind. Two RCTs evaluated pre-hospital cooling with cold IV fluids compared to standard care or in-hospital cooling. There was significant variability in the amount of IV fluids given in the pre-hospital setting; therefore, it is difficult to interpret the results. In the pre-hospital setting, it is likely to be an on-going difficulty to consistently initiate therapeutic hypothermia due to variables of transport time, staff resources, and re-arrest events in the ambulance. We found one RCT, the largest multi-centre RCT to-date, aimed at determining whether one lower body temperature was better than another. Unlike in other studies, which mainly focused on ventricular fibrillation and pulseless ventricular tachycardia only, the authors of this study included all initial rhythms in their cardiac arrest protocols. They had broader inclusion criteria in comparison to previous trials, which makes their results more generalisable to a diverse patient population. However, the ideal length of time for targeted temperature management remains unclear.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, February 2010, to November 2014. A back search from 1966 was performed for the new options added to the scope at this update. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 222 studies. After deduplication and removal of conference abstracts, 114 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 89 studies and the further review of 25 full publications. Of the 25 full articles evaluated, one systematic review included in a previous version was updated and three RCTs were added at this update.

ADDITIONAL INFORMATION

Therapeutic hypothermia is a resource-intensive intervention. It requires higher multi-disciplinary staff resources, higher intensity of monitoring, and potential management of adverse effects. The complexity of this procedure would make it difficult to effectively initiate in the pre-hospital setting due to limited staff resources. It should be noted that hypothermia can lead to coagulopathy, sepsis, severe electrolyte abnormalities, cardiac dysfunction, and prolonged ICU stays. Therefore, induced hypothermia cannot be regarded as being without risk.

DEFINITION

Ventricular tachyarrhythmias are defined as abnormal patterns of electrical activity originating within ventricular tissue. The most commonly encountered ventricular tachyarrhythmias, of greatest clinical importance to clinicians, are ventricular tachycardia and ventricular fibrillation. **Ventricular tachycardia** is further classified as monomorphic when occurring at a consistent rate and amplitude, and polymorphic when waveforms are more variable and chaotic. **Ventricular fibrillation** is characterised by irregular and chaotic electrical activity and ventricular contraction in which the heart immediately loses its ability to function as a pump. Pulseless ventricular tachycardia and ventricular fibrillation are the primary causes of sudden cardiac death (SCD). **Population** In this overview, we

© BMJ Publishing Group Ltd 2015. All rights reserved.

focus on therapeutic hypothermia (body temperature of 36°C or lower) with or without anti-arrhythmics for people with cardiac arrest in an out-of-hospital setting.

INCIDENCE/ PREVALENCE

The annual incidence of SCD has been estimated to approach 1/1000 in the population with a presumed cardiac aetiology. [5] It is believed that approximately 395,000 people suffer from out-of-hospital SCD annually in the US, suggesting that it is the third leading cause of death in the US. [2] Approximately 90% of out-of-hospital SCD is a result of cardiac aetiology, with an average of 20% having an initial shockable rhythm of ventricular fibrillation or ventricular tachycardia. [2] It has been reported that only 6% of out-of-hospital cardiac arrest patients survive to hospital discharge. [2]

AETIOLOGY/ RISK FACTORS

Ventricular arrhythmias occur as a result of structural heart disease arising primarily from myocardial ischaemia or cardiomyopathies. In resource-rich countries, ventricular tachycardia- or ventricular fibrillation-associated cardiac arrest is believed to occur most typically in the context of myocardial ischaemia. As a result, major risk factors for SCD reflect those that lead to progressive coronary artery disease. Risk factors for SCD include coronary artery disease, structural heart disease, and chronic obstructive pulmonary disease. [2] Male sex, older age, and racial and ethnic minorities are also risk factors, as well as other severe comorbidities. [2]

PROGNOSIS

Ventricular fibrillation and ventricular tachycardia associated with cardiac arrest result in lack of oxygen delivery and major ischaemic injury to vital organs. If untreated, this condition is uniformly fatal within minutes. In out-of-hospital cardiac arrest a variety of factors contribute to prognosis, including location of arrest, bystander CPR, time to return of spontaneous circulation, and pre-morbid risk factors. [2]

AIMS OF INTERVENTION

In conjunction with cardiopulmonary resuscitation and defibrillation, after restoration of sinus rhythm or a sufficiently organised electrical rhythm that will support the systemic circulation, the aim is to improve chances of successful recovery, improve neurological outcomes, and reduce mortality, with minimal adverse effects.

OUTCOMES

Survival/mortality, including survival to hospital admission and survival to hospital discharge; **functional neurological recovery**; **quality of life**; **adverse effects**.

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date November 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to November 2014, Embase 1980 to November 2014, The Cochrane Database of Systematic Reviews 2014, issue 11 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, and containing more than 20 individuals, of whom more than 80% were followed up. There was no minimum length of follow-up. We included all studies described as 'open' or 'open label'. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our pre-defined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following previously reported questions: What are the effects of electrical therapies for out-of-hospital cardiac

© BMJ Publishing Group Ltd 2015. All rights reserved.

arrest associated with ventricular tachycardia or ventricular fibrillation? What are the effects of antiarrhythmic drug treatments for use in out-of-hospital cardiac arrest associated with shock-resistant ventricular tachycardia or ventricular fibrillation? **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 14). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of lowering body temperature for comatose survivors of out-of-hospital cardiac arrest associated with ventricular tachycardia or ventricular fibrillation?**

OPTION **THERAPEUTIC HYPOTHERMIA (TARGETED TEMPERATURE MANAGEMENT) WITH OR WITHOUT STANDARD THERAPY (INCLUDING ANTI-ARRHYTHMICS)**

- For GRADE evaluation of interventions for Out-of-hospital cardiac arrest in adults: lowering body temperature, see table, p 14 .
- Therapeutic hypothermia initiated within 6 hours of hospital arrival in out-of-hospital cardiac arrest patients may increase the proportion of people that survive to hospital discharge.
- Therapeutic cooling may improve neurological outcomes in cardiac arrest.
- There is no clear indication for a specific cooling method to induce hypothermia.
- There was no statistically significant difference found in the rates of adverse events between the therapeutic hypothermia group and the normothermia group.
- There does not appear to be any benefit from pre-hospital cooling in out-of-hospital cardiac arrest.

Benefits and harms

Therapeutic hypothermia versus control/normothermia:

We found two systematic reviews (search dates 2009; [6] and 2011 [7]) assessing the effects of therapeutic hypothermia on comatose survivors of in- or out-of-hospital cardiac arrest. The reviews identified the same five RCTs (481 adults who suffered from cardiac arrest in or out of hospital [various causes] and were successfully resuscitated) that evaluated therapeutic hypothermia given within 6 hours of hospital arrival (target temperature 35°C or below): four of the RCTs evaluated treatment in people experiencing an out-of-hospital arrest (206 people), and in the other RCT almost 90% of arrests were out of hospital. The reviews presented different analyses of the data. The authors of the reviews acknowledged that there was variation across the identified RCTs in the methods used for cooling, including conventional cooling and haemofiltration. The most recent review analysed data by methods of cooling. [7] By contrast, the other review [6] analysed trials based on categorisation of risk of bias. For this reason, we report the results from the review analysing data by cooling method; see Further information on studies for more details about cooling methods. [7]

Survival/mortality

Therapeutic hypothermia compared with control/normothermia Conventional cooling during hospital stay given within 6 hours of hospital arrival may be more effective than control (defined as standard treatment at the time the trials were undertaken, which may include anti-arrhythmics) at increasing the proportion of people who survive to hospital discharge, but we don't know whether haemofiltration, as a specific method to achieve hypothermia, improves survival at 6 months (low-quality evidence).

© BMJ Publishing Group Ltd 2015. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Survival					
[7] Systematic review	Adults aged >18 years who suffered cardiac arrest in or out of hospital 3 RCTs in this analysis	**Survival to hospital discharge** 110/195 (56%) with therapeutic hypothermia (conventional cooling) 79/188 (42%) with control	RR 1.35 95% CI 1.10 to 1.65 P = 0.0038	●○○	therapeutic hypothermia
[7] Systematic review	Adults aged >18 years who suffered cardiac arrest out of hospital Data from 1 RCT	**Survival , 6 months** 7/22 (32%) with therapeutic hypothermia (haemofiltration) 9/20 (45%) with control	RR 0.71 95% CI 0.32 to 1.54 P = 0.38	⟷	Not significant

Functional neurological recovery

Therapeutic hypothermia compared with control/normothermia Conventional cooling during hospital stay given within 6 hours of hospital arrival may be more effective than control (defined as standard treatments at the time the studies were undertaken, which include anti-arrhythmics) at increasing the proportion of people with neurological improvement (defined as achieving cerebral performance categories [CPC] grade 1/2), but we don't know whether haemofiltration improves neurological outcomes at 6 months. Therapeutic hypothermia (conventional or other method) may be more effective than control at improving neurological function in people with out-of-hospital cardiac arrest or people with cardiac arrest with ventricular fibrillation/tachycardia (based on sub-group analyses) (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Good neurological outcome					
[7] Systematic review	Adults aged >18 years who suffered cardiac arrest in or out of hospital 3 RCTs in this analysis	**Proportion of people who achieved CPC grade 1 or 2 during hospital stay** 104/195 (53%) with therapeutic hypothermia (conventional cooling) 65/188 (35%) with control	RR 1.55 95% CI 1.22 to 1.96 P = 0.00027	●○○	therapeutic hypothermia
[7] Systematic review	Adults aged >18 years who suffered cardiac arrest out of hospital Data from 1 RCT	**Proportion of people who achieved CPC grade 1 or 2 , 6 months** 7/22 (32%) with therapeutic hypothermia (haemofiltration) 9/20 (45%) with control	RR 0.71 95% CI 0.32 to 1.54 P = not significant (reported inconsistently as 0.69 in text and 0.38 in figure)	⟷	Not significant
[7] Systematic review	Adults aged >18 years who suffered cardiac arrest out of hospital Data from 1 RCT	**Proportion of people with Glasgow Outcome Scale score of 1–3 , 1 month** 18/36 (50%) with therapeutic hypothermia (unknown method) 2/18 (11%) with control	RR 4.50 95% CI 1.17 to 17.30 P = 0.029	●○○	therapeutic hypothermia
[7] Systematic review	Adults aged >18 years who suffered cardiac arrest out of hospital 3 RCTs in this analysis Subgroup analysis Analysis by location of arrest	**Good neurological function** with cooling with control Absolute results not reported 365 people in this analysis	RR 1.56 95% CI 1.23 to 1.99 P value not reported	●○○	cooling

© BMJ Publishing Group Ltd 2015. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[7] Systematic review	Adults aged >18 years who suffered cardiac arrest with VF/VT rhythm in or out of hospital 2 RCTs in this analysis Subgroup analysis Analysis by initial heart rhythm	**Good neurological function** with therapeutic hypothermia with control Absolute results not reported 330 people in this analysis	RR 1.47 95% CI 1.15 to 1.88 P value not reported	●○○	therapeutic hypothermia

Quality of life

No data from the following reference on this outcome. [7]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[7] Systematic review	Adults aged >18 years who suffered cardiac arrest in or out of hospital 3 RCTs in this analysis	**Adverse effects** with therapeutic hypothermia (conventional cooling) with control The review reported no significant difference in adverse effects for therapeutic hypothermia compared with control			

Pre-hospital hypothermia plus standard care versus standard care alone:

We found two RCTs that evaluated the effects of pre-hospital hypothermia. [8] [9] Both RCTs compared pre-hospital cooling plus standard care (after return of spontaneous circulation [ROSC], intravenous infusion of 2 L of saline fluid at 4°C temperature) with standard care alone. [8] In both RCTs, once people arrived at hospital, people were treated at the physician's discretion [8] or as per hospital cooling protocol. [9] Therefore, for both RCTs, we have limited reporting of results up to hospital admission in the Benefits and harms section; post-admission results are reported in Further information on studies.

Survival/mortality

Pre-hospital hypothermia plus standard care compared with standard care alone We don't know whether pre-hospital cooling plus standard care is more effective than no pre-hospital cooling plus standard care (which may include antiarrhythmics) at increasing the proportion of people with out-of-hospital cardiac arrest who survive to hospital admission (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Survival to admission					
[8] RCT	125 resuscitated people with out-of-hospital cardiac arrest	**Survival to admission** 49/63 (78%) with pre-hospital cooling plus standard care	Significance not assessed		

© BMJ Publishing Group Ltd 2015. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		48/62 (77%) with standard care alone			
Death before admission					
[8] RCT	51 people with out-of-hospital cardiac arrest associated with ventricular fibrillation Subgroup analysis	**Death before hospital admission** 3/29 (10%) with pre-hospital cooling plus standard care 3/22 (14%) with standard care alone	Significance not assessed		
[9] RCT	1364 people with out-of-hospital cardiac arrest	**Death before hospital admission** 9/688 (1%) with pre-hospital cooling plus standard care 11/ 671 (2%) with standard care alone 583 people in this analysis had VF (292 in the cooling group *v* 291 in the standard care group)	P = 0.61	⟷	Not significant

Functional neurological recovery

No data from the following reference on this outcome. [8] [9]

Quality of life

No data from the following reference on this outcome. [8] [9]

Adverse effects

No data from the following reference on this outcome. [8] [9]

Further information on studies

[7] *Study quality* Two of the five RCTs included in the review had inadequate or unclear randomisation methods, and two had unclear information on blinding. It was noted in one of the RCTs that people in the normothermic group were more likely at baseline to have diabetes mellitus or coronary heart disease and were more likely to have had basic life support from a bystander compared with the hypothermia group. When the RCT authors adjusted for these baseline variables, a slight increase in risk ratio was noted. Another RCT noted baseline differences for sex and bystander CPR between groups.

[7] *Cooling methods implemented across the studies* The review noted that only three of the five trials used conventional cooling methods and were deemed to have been of good quality. Of the remaining two RCTs, one used haemofiltration and the other did not state their method of cooling. The study with unclear method of cooling was not included in any of the meta-analyses.

[8] The RCT reported that in the 62 people randomised to standard care alone, no cooling was performed pre-hospital; however, of the 63 people randomised to pre-hospital cooling, in fact eight people received no fluid,

© BMJ Publishing Group Ltd 2015. All rights reserved.

six people received less than 500 mL, 37 people received between 500 mL and 2 L, and 12 people received 2 L. This variation in the pre-hospital cooling protocol occurred because of death pre-hospital arrival, re-arrest, and lack of time before hospital arrival.

[8] *Survival at discharge* The RCT reported that pre-hospital cooling increased the proportion of people that had VF rhythm arrests who survived to hospital discharge compared with standard care; however, this difference did not reach significance (proportion who had VF arrests who survived: 19/29 [66%] with cooling *v* 10/22 [45%] with control; P value not reported; reported as not significant). [8] Of the 97/125 (78%) people admitted to hospital, 60/97 (62%) were treated at the discretion of the attending physician with hypothermia induced by surface cooling. The RCT hypothesised that the interaction of pre-hospital cooling and in-hospital cooling could impact on survival to hospital discharge. In an exploratory analysis of the 97 people admitted to hospital, the RCT found no significant difference for survival to hospital discharge between pre-hospital cooling alone and standard in-patient care (OR 1.25, 95% CI 0.55 to 2.82; absolute data not reported). Additionally, when the odds ratio was adjusted for hospital cooling and the interaction term (using a multiple logistic regression model) in those who received pre-hospital cooling alone, the likelihood of survival to discharge remained non-significant (adjusted OR 1.92, 95% CI 0.46 to 8.00; absolute data not reported); for those receiving hospital cooling alone there was also no significant difference in survival to hospital discharge compared with standard care (OR 0.91, 95% CI 0.28 to 2.96, adjusted for pre-hospital cooling and interaction term; absolute data not reported). The RCT found no significant interaction variable between pre-hospital and hospital cooling. [8] The RCT also reported a non-significant trend in favour of pre-hospital cooling in the proportion of people who awakened (proportion who had VF arrests: 20/29 (69%) with cooling *v* 10/22 (45%) with standard care; P = 0.15). [8]

[9] None of the people randomised to standard care alone (291 people with VF) received pre-hospital cooling. Most people randomised to pre-hospital cooling (292 people with VF) received 4°C intravenous saline. Around 50% of those randomised to pre-hospital cooling did not receive the full amount of fluid because of death, recurrent arrest, or lack of time before hospital arrival.

[9] *Post-admission results* The RCT reports that, of the people with VF who survived to hospital admission, 448 received in-hospital cooling after randomisation, irrespective of original treatment allocation: 224/448 (50%) people had received pre-hospital cooling, and the remaining 50% received standard care alone. The RCT found no significant difference between the two groups in survival to discharge in the subgroup of people with VF (63% with pre-hospital cooling *v* 64% with standard care, P = 0.69). There was also no significant difference between the groups in neurological status or for those who awakened from coma, in people with cardiac arrest associated with VF.

Comment:

Adverse effects

It should be noted that hypothermia can lead to coagulopathy, sepsis, severe electrolyte abnormalities, cardiac dysfunction, and prolonged ICU stays. [10] Therefore, induced hypothermia cannot be regarded as being without risk.

Pre-hospital hypothermia

There was significant variability in the amount of IV fluids given in the pre-hospital setting; therefore, it is difficult to interpret the results. In the pre-hospital setting it is likely to be an on-going difficulty to consistently initiate therapeutic hypothermia due to variables of transport time, staff resources, and re-arrest events in the ambulance.

Clinical guide

Earlier trials have proposed benefit from therapeutic hypothermia; however, these trials had variability in the temperatures achieved in the control group. New research, with tighter temperature controls in the study, suggest that targeting a temperature of 36°C shows equal benefit compared to therapeutic hypothermia. [11] There is no obvious advantage, based on current literature, to support pre-hospital cooling; moreover, there are concerns of harm associated with fluid overload from large amounts of intravenous fluid administered prior to hospital arrival. [12] It has been suggested that hyperthermia in post-cardiac-arrest patients has been detrimental; therefore, one aim of targeted temperature management is to actively avoid hyperthermia in this population. [12] Targeted temperature management is now considered the standard of care for these patient populations. For formal therapeutic guidelines, the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation has a formal publication statement for reference. [12]

OPTION **DIFFERENT LOWER BODY TEMPERATURES VERSUS EACH OTHER** New

- For GRADE evaluation of interventions for Out-of-hospital cardiac arrest in adults: lowering body temperature, see table, p 14 .

© BMJ Publishing Group Ltd 2015. All rights reserved.

- There was no significant difference in mortality when cooling to a target temperature of 33°C compared with 36°C. However, lowering body temperature to 32°C might be more effective than lowering to 34°C at reducing mortality at 6 months in people with a witnessed cardiac arrest with initial VF/VT or asystole (based on one small RCT).
- There was no significant difference found when comparing neurological outcomes at a target temperature of 33°C when compared with 36°C. However, lowering body temperature to 32°C seems to be more effective than lowering to 34°C at improving neurological outcome in people experiencing witnessed cardiac arrest (based on one small RCT).
- There did not appear to be any significant differences between serious adverse events when comparing 33°C with 36°C; however, there was a significant difference in rates of hypokalaemia among the 33°C group.
- We found no other RCTs comparing different target temperatures.

Benefits and harms

Different lower body temperatures versus each other:

We found two RCTs [11] [13] evaluating the effects of variation in low body temperature. See Further information on studies for detailed information on the cooling method.

Survival/mortality

Different lower body temperatures compared with each other Lowering body temperature to 36°C seems as effective as lowering to 33°C at reducing mortality in people experiencing out-of-hospital cardiac arrest, whereas lowering body temperature to 32°C might be more effective than lowering to 34°C at reducing mortality at 6 months in people with a witnessed cardiac arrest with initial VF/VT or asystole (based on one small RCT) (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[11] RCT	950 resuscitated people aged 18 or older with out-of-hospital cardiac arrest and who were unconscious on admission to hospital	**Deaths , after 180 days** 226/473 (48%) with cooling to 33°C 220/466 (47%) with cooling to 36°C	RR 1.01 95% CI 0.87 to 1.15 P = 0.92	⟷	Not significant
[11] RCT	950 resuscitated people aged 18 or older with out-of-hospital cardiac arrest and who were unconscious on admission to hospital	**Deaths , end of trial** 235/473 (50%) with cooling to 33°C 225/466 (48%) with cooling to 36°C	HR 1.06 95% CI 0.89 to 1.28 P = 0.51	⟷	Not significant
[13] RCT	36 people with a witnessed cardiac arrest with initial VF/VT or asystole 13 people in each arm had initial VF/VT rhythm	**Death , 6 months** 10/18 (56%) with cooling to 32°C 16/18 (89%) with cooling to 34°C All people with initial asystole died	P = 0.03	○○○	cooling to 32°C

Functional neurological recovery

Different lower body temperatures compared with each other Lowering body temperature to 36°C seems as effective as lowering to 33°C at preventing impaired neurological function in people experiencing out-of-hospital cardiac arrest, whereas lowering body temperature to 32°C seems to be more effective than lowering to 34°C at improving neurological outcome in people experiencing witnessed cardiac arrest (based on one small RCT) (moderate-quality evidence).

© BMJ Publishing Group Ltd 2015. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Neurological function					
[11] RCT	950 resuscitated people aged 18 or older with out-of-hospital cardiac arrest and who were unconscious on admission to hospital	**Neurological function (CPC of 3–5, 3 = severe disability, 5 = brain death) , at least 180 days' follow up** 251/469 (54%) with cooling to 33°C 242/464 (52%) with cooling to 36°C	RR 1.02 95% CI 0.88 to 1.16 P = 0.78	⟷	Not significant
[11] RCT	950 resuscitated people aged 18 or older with out-of-hospital cardiac arrest and who were unconscious on admission to hospital	**Modified Rankin scale score of 4–6 (4 = moderate severe disability, 6 = death) , at least 180 days' follow up** 245/469 (52%) with cooling to 33°C 239/464 (52%) with cooling to 36°C	RR 1.01 95% CI 0.89 to 1.14 P = 0.87	⟷	Not significant
[13] RCT	36 people with a witnessed cardiac arrest with initial VF/VT or asystole Subgroup analysis People with initial VF/VT rhythm	**Best neurological outcome measured on Pittsburgh cerebral performance category (scale 1–2, good or moderate disability) , 6 months** 9/13 (69%) with cooling to 32°C 3/13 (23%) with cooling to 34°C	P = 0.02	○○○	cooling to 32°C

Quality of life

No data from the following reference on this outcome. [11] [13]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] RCT	950 resuscitated people aged 18 or older with out-of-hospital cardiac arrest and who were unconscious on admission to hospital	**One or more serious adverse events** 439/472 (93%) with cooling to 33°C 417/464 (90%) with cooling to 36°C	RR 1.03 95% CI 1.00 to 1.08 P = 0.09	⟷	Not significant
[11] RCT	950 resuscitated people aged 18 or older with out-of-hospital cardiac arrest and who were unconscious on admission to hospital	**Hypokalaemia** 19% with cooling to 33°C 13% with cooling to 36°C Absolute numbers not reported	P = 0.02	○○○	cooling to a higher temperature (36°C *v* 33°C)
[13] RCT	36 people with a witnessed cardiac arrest with initial VF/VT or asystole	**Incidence of clinical seizures , 1 week** 1/18 (6%) with cooling to 32°C 11/18 (61%) with cooling to 34°C	P = 0.0002	○○○	cooling to a lower temperature (32°C *v* 34°C)

© BMJ Publishing Group Ltd 2015. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Subgroup analysis 13 people in each arm had initial VF/VT rhythm				

Further information on studies

[11] *Methods* Method of randomisation was robust. Outcome assessors, including the physician performing the neurological assessment, were masked to treatment.

[11] *Population characteristics* Most people enrolled had ventricular fibrillation, with 74% (349/473) in the group cooled to 33°C and 77% (356/466) in the group cooled to 36°C diagnosed as being in ventricular fibrillation.

[11] *Treatment* Cooling lasted 36 hours from the time of randomisation. The methods of cooling included ice-cold fluids, ice packs, and intravascular or surface-temperature-management devices. Gradual re-warming to 37°C was started in both groups after 28 hours, and temperature was maintained below 37.5°C until 72 hours after cardiac arrest.

[13] *Methods* Method of randomisation was robust. Those providing initial treatment could not be blinded but physicians assessing neurological outcome at 6 months were blinded.

[13] *Population characteristics* 26/36 (72%) of people enrolled (13 in each arm) had ventricular fibrillation or ventricular tachycardia. The remaining population enrolled were in asystole.

[13] *Treatment* Cooling was carried out through intravenous infusion of saline less than 8°C set to a maximum rate according to targeted temperature assigned at randomisation. Cooling was maintained for 24 hours, followed by gradual re-warming to 37°C over 12 to 24 hours. In addition, all participants received standard care.

Comment:

The RCT [11] was the largest multi-centre RCT performed to-date, aimed at determining whether one lower body temperature was better than another. The authors had a rigorous study design with a large sample size for the clinical question asked. Unlike in other studies, which mainly focused on ventricular fibrillation and pulseless ventricular tachycardia only, they included all initial rhythms in their cardiac arrest protocols. They had broader inclusion criteria in comparison to previous trials, which makes their results more generalisable to a diverse patient population. Furthermore, they were more comprehensive in blinding outcome assessors, authors, statisticians, and study administrations when compared to earlier RCTs. [3] [4] They found no significant difference in all-cause mortality and neurological outcomes when comparing a targeted temperature of 33°C to 36°C for a total of 36 hours. These results suggest that there is equal mortality and neurological benefit when targeting a temperature of 36°C, without the potential risks associated with hypothermia.

Clinical guide

The body of literature surrounding hypothermia as a cardiac arrest therapy has previously been supported. In contrast to earlier recommendations, [1] [10] new emerging literature supports targeted temperature management at 36°C and preventing hyperthermia. In fact, the International Liaison Committee on Resuscitation (ILCOR) have recently recommended selecting and maintaining a constant temperature between 32°C and 36°C in out-of-hospital cardiac arrest patients. [12] ILCOR also advises that targeted temperature management should be applied for a total of 24 hours. While keeping in mind that the evidence is strongest for VF/VT, targeted temperature management should be considered a therapy for other causes of cardiac arrest. [12] For formal therapeutic guidelines, the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation has a formal publication statement for reference.

OPTION DIFFERENT DURATIONS OF LOWER BODY TEMPERATURE VERSUS EACH OTHER New

- For GRADE evaluation of interventions for Out-of-hospital cardiac arrest in adults: lowering body temperature, see table, p 14 .
- We don't know how different durations of lower body temperature compare to each other in adults who are comatose survivors of out-of-hospital cardiac arrest, as we found no evidence.

© BMJ Publishing Group Ltd 2015. All rights reserved.

Benefits and harms

Different durations of lower body temperature versus each other:

We found no RCTs or systematic reviews.

Comment: The ideal length of time for targeted temperature management in adults who are comatose survivors of out-of-hospital cardiac arrest remains unclear at present.

GLOSSARY

Glasgow Outcome Scale (GOS) A 5-point scale widely used to assess outcome after head injury (or other brain injury). Score of 5 = good recovery (able to return to work or school); score of 4 = moderate disability (disabled but able to live independently); score of 3 = severe disability (dependent on daily support); score of 2 = persistent vegetative state; score of 1 = dead.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Modified Rankin scale A measure of disability after a stroke or other brain injury. Score 0 = no disability; 1 = no significant disability (able to carry out usual activities despite some symptoms); 2 = slight disability (no assistance needed but unable to carry out all previous activities); 3 = moderate disability (requiring some help but able to walk without assistance); 4 = moderate severe disability (requiring assistance to walk and to attend to body needs); 5 = severe disability (bedridden, incontinent, requiring constant nursing care); and 6 = death.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Different lower body temperatures versus each other New option. Two RCTs added. [11] [13] Categorised as 'unknown effectiveness'.

Different durations of lower body temperature versus each other New option. We found no RCTs or systematic reviews. Categorised as 'unknown effectiveness'.

Therapeutic hypothermia (targeted temperature management) with or without standard therapy (including anti-arrhythmics) One systematic review updated [7] and one RCT [9] added. Categorisation unchanged (likely to be beneficial).

REFERENCES

1. Nolan JP, Hazinski MF, Billi JE, et al. Part 1, Executive summary: 2010 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Resuscitation* 2010;81 Suppl 1:e1–e25.[PubMed]
2. Institute of Medicine (IOM). Strategies to improve cardiac arrest survival: A time to act. Washington, DC: The National Academic Press, 2015. Available at http://iom.nationalacademies.org/Reports/2015/Strategies-to-Improve-Cardiac-Arrest-Survival.aspx (last accessed 14 October 2015).
3. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346:557–563.[PubMed]
4. Hypothermia after Cardiac Arrest (HACA) Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346:549–556. [Erratum in: *N Engl J Med* 2002;346:1756.][PubMed]
5. Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. *Circulation* 2012;125:620–637.[PubMed]
6. Nielsen N, Friberg H, Gluud C, et al. Hypothermia after cardiac arrest should be further evaluated – a systematic review of randomised trials with meta-analysis and trial sequential analysis. *Int J Cardiol* 2011;151:333–341.[PubMed]
7. Arrich J, Holzer M, Herkner H, et al. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. In: The Cochrane Library, Issue 11, 2014. Chichester, UK: John Wiley & Sons. Search date 2011.[PubMed]
8. Kim F, Olsufka M, Longstreth WT, et al. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline. *Circulation* 2007;115:3064–3070.[PubMed]
9. Kim F, Nichol G, Maynard C, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. *JAMA* 2014;311:45–52.[PubMed]
10. Nolan JP, Neumar RW, Adrie C, et al. ILCOR Consensus Statement. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. *Resuscitation* 2008;79:350–379.[PubMed]
11. Nielsen N, Wettersley J, Cronberg T, et al; TTM Trial Investigators. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med* 2013;369:2197–2206.[PubMed]
12. Donnino MW, Andersen LW, Berg KM, et al; ILCOR ALS Task Force. Temperature management after cardiac arrest. *Resuscitation* 2015 Oct 5. [Epub ahead of print.][PubMed]
13. Lopez-de-Sa E, Rey JR, Armada E, et al. Hypothermia in comatose survivors from out of hospital cardiac arrest: pilot trial comparing 2 levels of target temperature. *Circulation* 2012;126: 2862–2833.[PubMed]

Kendra Houston
Cumming School of Medicine
University of Calgary
Calgary
Canada

© BMJ Publishing Group Ltd 2015. All rights reserved.

Eddy S. Lang
Attending Staff, Associate Professor
Cumming School of Medicine
University of Calgary
Calgary
Canada

Competing interests: KH and ESL declare that they have no competing interests.
We would like to acknowledge the previous contributors of this review, Kim Browning and Marwan A.l. Raisi.

Disclaimer

The information contained in this publication is intended for medical professionals. Categories presented in Clinical Evidence indicate a judgement about the strength of the evidence available to our contributors prior to publication and the relevant importance of benefit and harms. We rely on our contributors to confirm the accuracy of the information presented and to adhere to describe accepted practices. Readers should be aware that professionals in the field may have different opinions. Because of this and regular advances in medical research we strongly recommend that readers' independently verify specified treatments and drugs including manufacturers' guidance. Also, the categories do not indicate whether a particular treatment is generally appropriate or whether it is suitable for a particular individual. Ultimately it is the readers' responsibility to make their own professional judgements, so to appropriately advise and treat their patients. To the fullest extent permitted by law, BMJ Publishing Group Limited and its editors are not responsible for any losses, injury or damage caused to any person or property (including under contract, by negligence, products liability or otherwise) whether they be direct or indirect, special, incidental or consequential, resulting from the application of the information in this publication.

© BMJ Publishing Group Ltd 2015. All rights reserved.

GRADE **Evaluation of interventions for Out-of-hospital cardiac arrest in adults: lowering body temperature.**

Important outcomes	Functional neurological recovery, Quality of life, Survival/mortality								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of lowering body temperature for comatose survivors of out-of-hospital cardiac arrest associated with ventricular tachycardia or ventricular fibrillation?									
4 (425) [7]	Survival/mortality	Therapeutic hypothermia versus control/normothermia	4	–1	0	–1	0	Low	Quality point deducted for weak methods in 2 RCTs; directness point deducted for unclear intervention in 1 RCT, affecting generalisability
5 (481) [7]	Functional neurological recovery	Therapeutic hypothermia versus control/normothermia	4	–2	0	–1	0	Very low	Quality points deducted for weak methods in 2 RCTs and incomplete reporting in subgroup analyses; directness point deducted for unclear intervention in 1 RCT, affecting generalisability
2 (at least 1484) [8] [9]	Survival/mortality	Pre-hospital hypothermia plus standard care versus standard care alone	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and not all pre-hospital group receiving full intervention
2 (975) [11] [13]	Survival/mortality	Different lower body temperatures versus each other	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of some people without VF or VT (asystole) (1 RCT)
2 (965) [11] [13]	Functional neurological recovery	Different lower body temperatures versus each other	4	0	0	–1	0	Moderate	Directness point deducted for subgroup analysis in 1 RCT

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.

© BMJ Publishing Group Ltd 2015. All rights reserved.